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THE RESULTS OBTAINED FROM THE USE OF
ANILINE PRODUCTS IN THE TREAT-
MENT OF CARCINOMA.

By WILLY MEYER, M.D..

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PROFESSOR OF SURGERY IN THE NEW YORK POST-GRADUATE MEDICAL
SCHOOL AND HOSPITAL; ATTENDING SURGEON TO THE GERMAN
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IT seems to me not more than proper that in a discussion on carcinoma the treatment of inoperable malignant growths should find its place. For I am decidedly of the opinion and fully concur with those who maintain that it is inhumane and undignified in the medical man to simply discharge from his direct care the poor sufferers who are afflicted with a tumor inaccessible to knife or cautery, to leave them with a pitiful shrug of the shoulders to their inevitable fate. Never have I been more embarrassed than on being confronted with the necessity of telling a patient that an operation was inadvisable when he had come to my office or the hospital for the sake of having a large, painful, steadily-growing neoplasm removed. These patients should be *treated* on the same principles as patients afflicted with consumption or chronic nephritis or any other incurable disease. But not only should we prescribe for them the anodynes in different forms, or give them a nurse to regularly inject morphine hypodermically to alleviate their sufferings; not only should we satisfy ourselves with the attempt at improving their digestion and assimilation, to brighten them up and encourage them with words of hope and coming improvement, which will nearly always be

¹ Read before the Medical Society of the State of New York at its eighty-seventh annual meeting, Albany, February 8, 1893, being part of the "Discussion on Carcinoma."



nullified by the experience of the immediate future, but, we should aim to still attack the growth itself that can not be conquered any more by ordinary surgical means. We should try to make it yield to other modes of scientific warfare. In the case of cancer of the intestinal tract from the œsophagus down to the rectum, the physician, of course, will not tell his patient the exact condition. Manifold interesting operations are performed for this reason to-day, and will generally improve the condition of the patient. The poor sufferer is led gently down to his grave, often totally unaware of the nature of his trouble. But in tumors of head, face, neck and trunk beyond the control of ordinary means, the patient can watch and see the steady progress of the terrible foe. Inch by inch he has to give way in resignation or despair. Is it not our solemn duty to help in these instances by direct applications if there is the slightest hope of really doing any good by our interference?

The despair in these conditions is such as to lead every practitioner to confess that doctor and patient would eagerly grasp not only what would offer a promise of cure, but also anything which should afford even a chance of palliation.

Had it been left to me to select the subject of my paper in this discussion, I should have rather compared the value and results of the main methods which have been proposed up to date for the direct treatment of inoperable malignant tumors, viz.:

(1) Of the effect of the aniline dyes, especially the blue pyoktanin, in these cases;

(2) Of the inoculation of erysipelas;¹

(3) Of the newest, the hypodermic application of neurine.²

But my share has been given to me: I am to speak on the results obtainable from the use of aniline products in the treatment of carcinoma. Let me add at once the word "inoperable," because it is self-understood and cannot be emphasized too strongly that *operable* cases have always to be submitted

¹ See the very interesting and important paper of William B. Coley: The Treatment of Malignant Tumors by Repeated Inoculations of Erysipelas, with a Report of Ten Original Cases, American Journal of the Medical Sciences, May, 1893.

² A. Adamkiewicz, Untersuchungen ueber den Krebs, und das Princip seine Behandlung Wien. Wilh. Braumüller, 1893.

to radical extirpation, and should under no condition be treated otherwise. An early thorough removal of an early diagnosed malignant growth will, as it seems at present, forever remain the best and safest treatment we can bestow on our patients. A general treatment with an anti-cancerous remedy, if scientifically established as such, may then follow.

On January 30, 1891, Prof. von Mosetig-Moorhof read a very interesting paper before the Vienna Society of Physicians, "A Contribution to the Treatment of Inoperative Malignant Growths," in which he reported on his experience with blue pyoktanin in such cases. Having read his publication, and being myself at that time engaged in experimenting with another aniline dye, the fuchsine, by external application in two of my patients with ulcerating facial neoplasm at the country branch of the New York Skin and Cancer Hospital,³ I at once followed his advice and began to inject the blue dye parenchymatously. I was convinced that if von Mosetig-Moorhof earnestly recommended a treatment for this trouble and even presented his patients to the Vienna Society of Physicians to demonstrate the results of this treatment, we could rely upon him. Let me say that von Mosetig-Moorhof is the same gentleman who thirteen years ago gave iodoform to the medical profession for surgical use and at the first maintained that it was a real anti-tubercular agent. Nearly every one doubted the latter assumption at first or was unable to find it, until at last it was shown, by careful experiments and observation that there is at present no better anti-tubercular remedy at our disposal in surgery. My first experience with the aniline dyes was laid down in my article, "Notes on the Effect of the Aniline Dyes, especially the Blue Pyoktanin, in the Treatment of Inoperable Malignant Growths," which appeared in the *New York Medical Record*, April 23, 1891. To-day I have been designated by our esteemed president to give you a *resumé* of the additional experience which has been gathered since that time by others and myself in this special line of treatment.

The literature on the subject is already quite extensive. The main part^a of it will be found at the end of this article.

³ N. Y. Med. Journal, April 11, 1891; Report of N. Y. Surgical Society, Meeting of February 25.

Pyoktanin is a representative of the large chemical group of methyl-violets which are now so very much used for different purposes in medical science; thus, for instance, for the staining of specimens in microscopical pathology. It derives its name "pus-killer" from its great antiseptic power, and was thus baptized by J. Stilling, Professor of Ophthalmology at the University of Strassburg, Germany, who, together with Dr. Wortmann, made careful bacteriological and chemical researches with the different aniline dyes.¹ Two kinds of pyoktanin are in the market, a blue and a yellow one (pyoktaninum cæruleum and p. aureum). The latter's antiseptic power is by far smaller. In mentioning "pyoktanin" in this paper, the blue drug is always meant.² It forms small crystals which are easily soluble in water.

A very handy shape of the pure drug is the pyoktanin pencil (large and small size). If dipped in water and then rubbed on the surface of a sore, ordinary, cancerous or sarcomatous, it easily makes a crust, a dry eschar, under which cicatrization often rapidly goes on. On an ulcerated surface an ointment application is preferable, 2, 5, 10. and more per cent.³ Fuchsin salve has in my hands been more useful than one containing pyoktanin. Other preparations are pyoktanin tablets, gauze, cotton, etc.

The standard solution for parenchymatous injection is 1-500.⁴ It forms no sediment if filtered through heated asbestos. The solution is to be kept in a dark bottle with glass or rubber stopper. Only a small quantity, about one ounce, should be prepared at the time. Still better is it to prepare it fresh for each injection. For external application in moist dressings a higher percentage can be applied.⁵ Even the pure drug may be dusted

¹ Anilin-Farbstoffe als Antiseptica u. ihre Anwendung in der Praxis, 2 Mittheilung, Strassburg, 1890.

² It is manufactured by Merck & Co. Their preparation is reliable and chemically pure.

³ Three parts of unguentum diachyli simpl. and one part lanoline is a good formula (v. Mosetig-Moorhof); also three parts lanoline and one part white vaseline.

⁴ Others have used it as strong as 1:300-1:100. Still it seems that 1:500 is the advisable percentage.

⁵ For ulcerating growths also in cavities (vagina) a 1-2 per cent. creolin-pyoktanin solution (equal parts) is recommended, especially if the tumor is in a state of decomposition.

on a sore surface, as it is not an irritant and absolutely non-poisonous. It is no deodorizer, and is itself inodorous. It has no styptic qualities. Its application in many cases is followed by a diminution of pain.

For parenchymatous injections the blue pyoktanin seems so far the most preferable of the aniline dyes.

I once injected the fuchsine—which often shows so very good results in external ointment application on ulcerating growths—to the extent of 1 per cent. every second or third day in a case of recurrent cancer of the breast in an unmarried lady of thirty-five. The local effect was for a number of weeks remarkable. The recurring tumor in the breast did not spread as far as the naked eye could perceive, but during the treatment a cancerous nodule in the other breast appeared, and when after ten weeks I had to stop the injections for special reasons, the patient died of cancer of the liver with a rapidity that I have never seen equalled in a patient suffering from this trouble. I shall never use fuchsine again for parenchymatous injections. It seemed as if in this case the injections had favored the metastasis of the cancer.

If injected into the tissue the pyoktanin solution either remains at the spot for some time or it leaves the tissue by diffusion, and then by way of the lymphatics enters the blood. The latter takes place if only a small quantity of the dye is injected. No harm has ever been done by it. If more abundantly injected diffusion cannot take place or only to a small degree. The dye remains *in loco*. The deeply-stained protoplasm dies.¹

The *technique* of the injection differs according to the locality. Still a number of general rules can be established and have to be borne in mind.

The injections have to be made under strict aseptic and anti-septic precautions.

The skin where the injection is going to be made must be carefully washed and then cleansed with ether.

The needles (long, short, curved and not of too small a calibre) must be boiled after using and then kept in alcohol.²

¹ As it appears, the drug applied in this way does not affect the healthy tissue, but only brings about a necrobiosis of the neoplastic tissue.

² A special needle with a number of lateral holes may be used.

The syringe is an ordinary well-working aspirator which holds two drachms. Before and after the injection it is washed inside and outside with a 5 per cent. carbolic solution. It shall be used only for this purpose.

The amount of the solution injected varies from one-half to three drachms, according to the size of the growth.

The spot where the needle entered is to be compressed after the withdrawal of the needle with a ball of moist antiseptic cotton until all oozing has ceased. It is then rubbed with ether and covered by a small piece of antiseptic gauze, fastened by pyoktanin—or iodoform—or ordinary collodium. Any other dressing is superfluous.

It is wise in the beginning of the treatment to distribute the dye through the entire tumor as rapidly as possible. The injections are, therefore, better made every other day, later every third day regularly.

Stilling proposed, in order to do this,¹ “to make use of the well-known method of von Nussbaum, who tied the arteries which fed the neoplasm in order to stop its growth. The tissue thus having been made bloodless first, should then be thoroughly dyed in all its parts and that as rapidly as possible.” I have followed his advice in the case of a pulsating osteosarcoma of the femur, which had already perforated the periosteum and begun to spread diffusely into the surrounding tissue. Patient, a man aged forty-four years, from Ogden, Utah, was utterly opposed to exarticulation at the hip, which, at the same time, gave little promise for a radical cure. The femoral artery was tied right below Poupart’s ligament at the German Hospital on April 30, 1891. This stopped the pulsation of the tumor. On the following days pyoktanin solution 1-300 in larger quantities, three to four drachms at a time, was regularly injected and care taken to distribute the fluid evenly and thoroughly. At different spots the tissue broke down. After a number of days a few smaller foci perforated spontaneously; a larger one had to be opened (lanced) with the knife. The sinuses discharged blue fluid (see further down) for some time and then closed (!) under the repeated use of the pyoktanin pencil. I then treated the patient regularly every second or third day with pyoktanin injections (1-300) for the following three

¹ Wiener klinische Wochenschrift, 1891, No. 2.

months, and had the distinct impression that the tumor which had formerly made a continuous rapid progress did not spread as far as visible. Unluckily the pulsation reappeared after some time. This new collateral circulation influenced the prognosis unfavorably, of course. When I left the city for my vacation local treatment was stopped and not resumed at the patient's home, whither he went at that time, in spite of my urgent advice to have it attended to. About nine months later I was informed that he had slipped and fallen on the street. A large swelling had formed in the region of the hip. Walking or standing was rendered impossible. I presume that the patient had fractured the (infiltrated?) neck of the diseased femur. The soft and bloody, rapidly-growing neoplasms, especially those of the bones, belong to a class of tumors which generally react very little, if at all, from the pyoktanin treatment. In this case the artificially depressed blood supply, immediately followed by rapid, diffuse pyoktanin dyeing and later by the ordinary treatment (injection every second or third day) certainly had a visible, beneficial effect on the spread of the growth as long as the patient remained under treatment.

In handling inoperable neoplasms which are directly accessible, the needle is best pushed into the healthy tissue about one-third of an inch from the border-line and then conducted forward and downward toward the base in an oblique direction. To save pain I generally advance from the same point in different directions. To do this the needle must always be retracted to the subcutaneous connective tissue and there turned. According to the size of the tumor, the calibre of the syringe and the surgeon's plan of treatment, this procedure is repeated at different spots at the same sitting.

If the growth is large and projecting, not only the bordering zone, but its tissue itself is attacked. Then I generally use a long needle and repeat the same procedure at different spots in the same sitting. The needle is introduced in its full length and then slowly retracted while the piston is pushed gently down.

With reference to the amount I am not so very particular. I have often injected four and five drachms in one sitting without the slightest detriment to the patient's general condition. Only care must be taken to distribute the fluid thoroughly and equally.

If too large an amount of the solution is deposited in a special area of the growth the tissues will break down rapidly.

It had been feared (Stilling) that the pyoktanin, if entering the blood in too large an amount, would dye the red blood-corpuscles and endanger their function. I believe with von Mosetig this fear to be groundless. In many hundreds of injections, pushing the daily dose up to four and five drachms of the solution 1-300, I have also never seen any symptoms which could be attributed to such an occurrence. I only remind of the internal use of methyl-blue, which can be given in ten-grain doses (0.6) and more daily without any detrimental general effect. Of course the solution for parenchymatous injection must be filtered. If this is not done undissolved pyoktanin crystals may produce emboli of the capillaries. It is evident that we have to be especially cautious in guiding the needle in the neighborhood of large blood-vessels. Von Mosetig lost one of his patients, a man with a sarcoma of two fists' size in the parotid region and the side of the neck, by an uncontrollable venous hæmorrhage. Post-mortem revealed that the superficially ulcerating neoplasm had infiltrated the wall of the internal jugular vein. Its breaking down at this spot had then given free exit to the venous blood. Von Mosetig concludes that we should avoid injection into tumors which involve large veins, also into those which cannot easily be reached by the needle.

If disseminated nodules are present I formerly injected their base. I have never succeeded in dyeing such a nodule by direct injection.

I believe that the rapid disappearance of the small hard nodules, which has sometimes been observed after parenchymatous injections (von Mosetig, author) does not mean reabsorption, but is an illusion which is caused by the œdema following the injections. A number of the nodules reappear soon after, sometimes rather multiplied.

As it seems the disseminated cancer (cancer *en cuirasse*) is no object for the aniline treatment.

In ulcerating growths the sore should be tamponed before the injection, or at least compressed with aseptic gauze or moist cotton during the manipulation lest the fluid should at once be

lost by that exit. The ulcer itself is rubbed with the pyoktanin pencil, or dusted with the dye in substance, or, if of offensive odor, dressed moist with the 1-2 per cent. solution of creoline and pyoktanin. The ulcerating surface should never be selected as the point of entrance for the needle, not even after very careful irrigation. The needle may convey septic material with it into the depth and set up inflammation. This is especially important in cases of cancer of the tongue, etc. This rule must be strictly observed.

In carcinoma of the cervix and body of the uterus no longer accessible to the knife, the method is somewhat complicated. Von Mosetig, Bachmaier and lately Boldt, of New York, have described it: The cancerous tissue is first thoroughly removed with the sharp curette, the bleeding surface tamponed with dry iodoform gauze. Twenty-four to forty-eight hours later the gauze is removed, and after proper disinfection of the operating field the injections are begun.¹ A long syringe is required. At last dry pyoktanin powder (or handier, as I believe, a small pencil) is introduced into the uterine cavity and a large-sized cotton tampon put in front of the cervix. An occlusion

¹ Boldt describes the procedure as follows: "The patient being placed in proper Sims's position and with the respective speculum and a Hunter's depressor, both *brightly* polished and applied *correctly*, one can readily see the entire uterine cavity *after* the curetting. The parts must then be thoroughly dried with aseptic absorbent cotton. Now the needle . . . is introduced. At the fundus uteri, the syringe having been filled with an aqueous solution of pyoktanin (blue) 1-100, the needle is inserted from 0.5 centimetres (one-fifth inch) upward, even to its full length, according to circumstances; *i. e.*, the thickness of the respective part where the injection is made; and while pushing the needle deeper the fluid is gradually pressed out by the piston, so that the deeper tissues are infiltrated with fresh staining fluid. One syringe-ful of pyoktanin solution is made to answer for two or three punctures. Next the liquid is injected into the parametria on either side, then the posterior vaginal wall, and last the anterior infiltrated vaginal wall; sometimes making as many as fifteen punctures at one sitting. I begin with the injection at the most distant part, because on withdrawal of the needle some of the fluid returns through the needle puncture and at once discolors the tissues immediately surrounding; so, were this to occur more proximally, the field for work would become so clouded that the injections could not be made with the requisite amount of precision." Boldt had a total of thirteen cases. All improved except two. The progress of the growth, if any took place, was much slower than it would be if the disease were left to pursue its course without this treatment,

pad must be worn, for even with the greatest care the clothing becomes somewhat soiled. The treatment is repeated every second day.¹ Cancerous nodules of the vagina are attacked as those of the surface of the body.²

That a malignant tumor of the œsophagus, stomach and intestinal tract, of the large intra- and retro-peritoneal glands is inaccessible to the needle is obvious. Happily the rapid strides of operative surgery within the last years, as gastrostomy, jejunostomy, colostomy and the manifold attempts at establishing an anastomosis between the different portions of the intestinal tract often produce such a wonderful temporary improvement in these cases, that many a patient dies after months of comparative comfort and satisfaction without having ever known that he had been afflicted with an incurable disease. Here (as well as in all other cases of carcinoma) the aniline dyes may be given internally in gelatine capsules. In my experience methyl-blue (Merck) is then the preferable drug. Pyoktanin is not well borne by the stomach.³ The daily doses may be pushed up to ten, twelve and more grains.

¹ Before the patient calls at the doctor's office the cotton is removed at home with the help of an attached string and a douche of several quarts of warm water used (Boldt).

² A few months ago I saw, in consultation with Dr. L. Fischer of this city, a woman of about forty-five years, with a far gone ulcerating cancer of the uterus (cauliflower) and vagina. Bleeding was profuse, odor very fetid, patient confined to bed. Continuous tamponade of the vagina with aseptic gauze, moistened in creolin-pyoktanin solution (2 per cent. $\bar{a}\bar{a}$) was agreed upon. As Dr. Fischer kindly notified me on inquiry (July 30): The patient now has "no pain, which formerly was one of her first severest symptoms. She has not emaciated; on the contrary she is gaining flesh. She has a good appetite, sits up occasionally. Odor and profuse discharge disappeared since third week of treatment. Bleeding rare; no inconvenience. Vaginal examination shows distinct presence of carcinoma." I almost doubt that creoline alone would have produced such an effect.

³ Methyl-blue was first used internally by Ehrlich (Ueber schmerzstillende Wirkung des Methylenblau, Deutsche medicinische Wochenschrift, 1880, No. 23). Lang saw good effect of its internal administration in cases of cystitis and pyelitis (Wiener klinische Wochenschrift, 1891, No. 6, p. 112). Methodical internal application of methyl-blue as a help in hopeless cancer cases was first tried and recommended by Drs. J. Rudisch and M. Einhorn of this city (New York Medical Record, March 21, 1891, Correspondence). The latter pronounced it an effective drug also in a certain percentage of cases of urinary troubles (gonorrhœa, pyelitis, etc.), and chronic skin diseases (New York Medical Record, Correspondence, 1891, p. 643). Lately it has

The drug will dye the urine from a light green at the beginning to a deep blue color.¹ The patient should be told that this will occur. Timid persons might else be easily frightened. If bladder tenesmus is caused by the larger doses, a tip of a knife full of nutmeg powder, scraped from the surface of a divided nut, or some carbonate of magnesia will generally help. In cancer of the pylorus von Oefele² saw good results (lessening of abdominal pain, gain of appetite and consequently weight) from the internal use of pyoktanin. He ordered his patients to take a gelatine capsule, containing one-sixth of a grain of cocainum phenylicum and one and a half grains of antifebrine into the empty stomach early in the morning. Four hours later, after a light breakfast, a large capsule with a 2 per cent. alcoholic pyoktanin solution was taken (amount in each capsule is not stated).

If the bladder be the seat of an inoperable cancer, irrigation with pyoktanin solution 1 : 1000, better 1 : 2000 or 3000 every third day may be tried. In two such cases of von Mosetig the transparency of the urine and the constant tenesmus were evidently improved and the hæmaturia ceased. (I have had no opportunity lately to use pyoktanin in patients afflicted with an inoperable tumor of the bladder, but I have often done so in cases of chronic (gonorrhœic) catarrh of the posterior urethra and bladder. There 1 : 3000 not infrequently created intense

been recommended by P. Guttman and P. Ehrlich, of Berlin, as the best specific against malarial fever (Ueber die Wirkung, des Methylenblau bei Malaria; Berliner klinische Wochenschrift, 1891, No. 39), which statement has since been confirmed by many authors. I have now and then observed a very beneficial subjective effect by the internal administration of methyl-blue (Merck) in patients who suffered from inoperable carcinoma. They claimed to feel brighter and more vigorous since taking the drug. I cannot well imagine that this should be due in every one of these cases to the anti-malarial effect of methyl-blue, although this cannot be denied. The proper maximum dose *pro die* seems to be about ten to fifteen grains. Yet higher doses have been given. They sometimes produce, however, acute albuminuria. It is best administered in capsules, each containing $1\frac{2}{3}$ –3 grains (1–2 decigrammes).

¹ It may be of interest to state, that the dye never enters the saliva and perspiration. The parenchymatous injection, even of large amounts of pyoktanin solution, does not color the urine. This is, perhaps, a proof for the assumption, that the dye remains for some time in the tissues, in which it had been deposited. However, I have often seen that pyoktanin, if internally administered, does not color the urine.

² Reichs Medicinal Anzeiger, June 19, 1891, No. 13.

burning; 1 : 10,000 was still of value. The dose was then gradually increased. I must confess, that the effect of the drug in a number of these cases was remarkable, though it failed in some.) Lately "a case of poisoning by methyl-blue" has been published by Z. Drzewiecki,¹ of Warsaw, Poland. Why Drzewiecki calls the symptoms, evidently caused by the dye, "poisoning," I cannot see. They only point to a marked irritation of the bladder, produced by continued large doses of the drug.

In impermeable cancerous stricture of the rectum or sigmoid curvature, where I had performed inguinal colostomy, repeated enemata with pyoktanin solution 1 : 3000 : 4000 with the patient in knee-elbow position, made the neoplasm break down rather rapidly; I have seen this in two patients. The obstruction was thus removed so that the lower end of the gut could be easily cleansed. These irrigations produce, however, a very annoying tenesmus, sometimes so much that the patients refuse to use them any further. In inoperable cases of cancer of the rectum, von Mosetig applied pyoktanin ointment tampons after preliminary superficial curettement.

Now, what are *the effects* of the aniline dyes as observed during the treatment and how can they be explained?

As in my first preliminary communication on this subject to the New York Surgical Society (March 13, 1891), I shall divide the effects—of course, provided that any set in—into subjective and objective.

(1) The "analgesic" effect is, evidently, the most important among the subjective effects.

Patients who, on account of continual pain have long become victims of the morphine habit, declare after the first parenchymatous injections, which may have been quite painful first on account of the suddenly increased intraparenchymatous pressure: "Doctor, what did you do with me? My pains are so much less. I slept in the last nights better than for many weeks." And this lessening of pain is not of a passing character. It becomes more apparent the longer the treatment is adhered to.

¹ New York Medical Record, 1893, No. 7, p. 202.

It is, therefore, not exceptional that in such cases the hypodermic syringe is soon laid aside and natural sleep refreshes and stimulates and brings new hope to the poor sufferer.

If a patient is afflicted with an ulcerating neoplasm, especially epithelioma of face and scalp, the aniline dye is applied in the form of a salve, or dusted on as a powder, or rubbed on the raw surface with the moist pencil. Not very rarely we will hear the remark after some time: "Doctor, of all the many treatments I have had, this is the best." I believe the drug has still to be found which can produce the same beneficial effect!

And what is the probable explanation of this occurrence? It is, as it seems, given in the experiment of Ehrlich, who proved, that living nerve tissue is dyed first and quickest. The latter, evidently, ceases to be a conductor until it has freed itself of the dye by diffusion. Before this can have taken place, the next application has already been made.

A direct consequence of this main and most striking effect is

(2) One of not less importance to the patient, "the improvement of function of the part involved."

I shall never forget the second call at my office of an unmarried lady, teacher in a public school,¹ who had an inoperable recurrent cancer of the breast. "O, doctor," she said, "my arm had been bent down to the chest for weeks and now already after one injection I can move it more freely." This functional improvement, which certainly was not imaginary, continued and increased the longer the treatment was adhered to and with additional use of massage and gymnastic exercises. The patient was even able on different occasions to comb her hair and button her dress in the back, which had previously been impossible. Von Mosetig states: "Patients, whose tongue had been immovable on account of cancerous infiltration could, after parenchymatous injection with pyoktanin, move it easier, could talk better, could chew and swallow with less trouble; in cases of large neoplasms of the neck, which had necessitated a forced, stiff position of the head, the latter could soon be moved without also turning the trunk; women with inoperable cancer of the uterus, who had

¹ The case has been mentioned above: fuchsin injections.

been confined to bed, could get up and walk around and often do light work in the household." The latter was also seen by Bachmaier.

Is it to be wondered if a patient beneficially reacts upon the aniline treatment, that less pain (without the use of morphine) and improved function induce better appetite and assimilation, that strength and weight increase, that in one word

(3) the general condition often shows an unmistakable change for the better?

Is it further to be wondered at; and can there at the same time be anything more gratifying than to see

(4) these poor, pitiable fellow-beings gain new hope, to observe their brightened eyes and their cheerful willingness to punctually subject themselves to a long-continued, sometimes painful, treatment? This treatment requires a decided exertion of will on the part of the patient, because the often-repeated prick of the needle, as well as the forced deposit of a certain amount of fluid in an area, which is often already infiltrated, naturally creates some pain. But how powerful this will becomes, even in the weak. It is therefore in my mind decidedly correct and only humane to assure these patients also of a continued *objective* improvement, even if the treatment, *once started*, does not produce the desired effect to the medical eye. A few encouraging words by the doctor will still more increase this favorable mental impression of the pyoktanin treatment.

With reference to the *objective* symptoms we observe general and local.

General symptoms, *very* rarely seen, are: Nausea or vomiting, weak and slow pulse, headache, general malaise. They may set in after intraparenchymatous injections, also after the internal use of methyl-blue. They appear on the same day or the day following the injection. As a rule, they do not come at all. Now and then there is a slight rise of temperature, usually subsiding within twenty-four to forty-eight hours. This may be due to imperfect asepis. In no case did the injections ever prove really harmful to the patient.

The local symptoms are different in ulcerating growths and in those still covered with healthy skin.

In the first it will often be seen, especially in rodent ulcers, if the dye be applied in solution or in a salve, that the sore surface soon presents a more healthy, rather granulating appearance. The former nasty discharge becomes scanty, at the borders cicatrization sets in.¹ If pyoktanin is dusted upon the surface in substance or thoroughly rubbed in with the wet, large pencil, an eschar forms. This comes off in the shape of dry gangrene without suppuration. Cachexia is thus held in check. Small growths can definitely cicatrize under this eschar in a number of weeks (epithelioma of nose and eyelid, Stilling). If the infiltrated margin of an epithelioma of the face (rodent ulcer) be injected, the tissue generally breaks down, the ulcer first seems to spread rapidly. But it only breaks down as far as the infiltration goes. If healthy tissue be reached the antiseptic properties of the aniline dyes can take effect, the ulcer begins to heal.

Did the neoplasm already invade the deeper tissues, a marked improvement can not be expected from this treatment. It has been seen (von Mosetig, author) that now and then disseminated small cancer nodules rather rapidly appear in the neighborhood of the hard border-line of a facial epithelioma, if the latter be treated with injections. According to my experience, we will do best not to deposit the dye parenchymatously in these cases, but to satisfy ourselves with applying it on the sore externally.

In unbroken neoplasms we observe after parenchymatous injections the following symptoms:

(a) *Edema* of the injected part and its neighborhood.

It appears either acutely and then often accompanied with slight redness (non-inflammatory) and pain on pressure, or more often in a subacute form. The oedema can remain for a long time. At last it disappears without interference, quicker with the help of gentle massage. Its presence is most probably due to the compression of the smallest veins by the dye which is

¹ It is fair to state here that such changes of a rodent ulcer of the face can be observed under manifold treatment, provided the latter be conducted on antiseptic principles. Only very lately von Bergmann has again called attention to this fact (Berliner klinische Wochenschrift, 1893, No. 28, p. 685). This effect of the aniline dyes, therefore, is not a specific one.

deposited in the parenchyma and can remain *in loco* for weeks without being reabsorbed (von Mosetig).

(b) *Breaking down* of the injected tissue (softening) with perforation of the skin.

This seems to set in more rapidly in using stronger solutions (1 : 200 or 100). A sinus or a number of sinuses are established which give exit to a thick dark-blue fluid. Microscopical examination proves this to be débris of the injected neoplasm, not colored pus.¹ Sometimes a few of these softened foci join and form a swelling of about hen's-egg size, which, of course, creates pain on account of intraparenchymatous pressure. Then the surgeon has to open it, but not by a long incision, as splitting the roof of an abscess, but by a small puncture hole, just sufficient to let out the dyed fluid. Under proper antiseptic treatment these sinuses will discharge the same blue fluid for some time and "then close." The tumor later will be found to have materially shrunk in such spots. If the sinus persists and pus escapes, infection has taken place. Then, of course, the patients are by far worse off than if nothing had been done. This point was especially emphasized by Billroth.²

¹ In one of my cases (recurrent cancer of breast) careful microscopical examination of this fluid was kindly made by Dr. I. Adler, of New York. The doctor's report reads as follows: The fluid, of pale violet color and containing small scraps of a solid matter, which formed an uneven and irregular sediment, was submitted to microscopical examination, and showed the following:

(1) A colorless, serous, slightly viscid fluid. In this fluid were suspended globules of free fat in great profusion and of all sizes; fat-crystals; innumerable leucocytes of all kinds, principally, however, of the large polynuclear species; a comparatively small number of red blood-corpuscles, all these of natural appearance and entirely unstained. Furthermore, large masses of granular amorphous detritus, either suspended loosely throughout the fluid or else gathered together into more compact masses. These latter were sometimes diffusely stained of a very pale, grayish-violet tint.

(2) The solid particles, which consisted of portions of fatty tissue and of patches of epithelial cells. The fatty tissue showed the regular polygonal fat-cells, sometimes emptied of their contents, sometimes filled with them. In either case a distinct and diffused bright violet-staining of the membrane could be made out, while the fat itself never showed any color. The epithelial cells were of the large, irregular, flat pavement species, either singly or in groups. Wherever an epithelial cell was found, it was at once recognized by its deep saturated stain. The coloring was entirely diffuse, and no nucleus could be made out without the aid of acids.

² Vienna Society of Physicians, March 13, 1891. Wiener klinische Wochenschrift, No. 12, p. 236.

(c) Breaking down (aseptic necrobiosis) or regressive fatty metamorphosis of the injected tissue with subsequent reabsorption (*i. e.*, without perforation of the skin).

It was proved by microscopical examinations [von Mosetig l. c. (Riehl, Zerner, Jun.), author, l. c. (I. Adler)] that the pathogenic cell elements are dyed by pyoktanin in the living body. The same occurs with normal connective tissue, muscles, nerves, glands. But whereas the physiological tissue with its biologically more powerful cell energy is not in the least altered by this coloring, rather quickly rids itself of the dye by diffusion, provided the dye is not forced into the cell in too large a quantity, the neoplastic elements succumb, and this the sooner the oftener they are attacked.¹

This simple, "mechanical" explanation seems the most plausible: We color the living protoplasm of the tumor so thoroughly that it breaks down and thus is destroyed.

A large tumor, however, if injected, does not soften or break down in every spot. Still we get in a number of cases the impression during the treatment that the neoplasm's further spread is arrested (fatty degeneration and reabsorption?).

To explain this latter phenomenon—the arrest of further growth with subsequent shrinking—von Mosetig had first hoped to find in microscopical sections of freshly and only once stained malignant tissue the nuclei of the cancer cells colored. He is of the opinion that the cancer cell is an epithelial cell, and that life and death of the nucleus determine proliferation or death of the cell. But he was first greatly disappointed, rather embarrassed, to find on microscopical examination the nuclei, as well as the cancer cells themselves, unaffected by the dye, whereas connective tissue and muscular fibres appeared stained. However, if the specimen was left exposed to the air the entire cut surface

¹ That this really happens could be nicely seen in one of my cases, a woman with a recurrent inoperable cancer of the breast, where after pyoktanin injections a number of fistulous tracks had formed. When they were split under ether a thick ramified mass of a deep blue color was found lying within normal, uncolored, slightly-indurated tissue. This evidently necrosed tissue could be easily shelled out with the finger or the sharp spoon; in many spots it still adhered to its surroundings. (See above, Dr. Adler's report.)

slowly turned violet without additional dyeing. How to explain this interesting phenomenon? The chemical experiment shows that hydrogen discolours a methyl-violet solution, the blue or violet aniline is reduced to white, the so-called leukaniline. The latter easily combines with oxygen and soon takes the blue color again.¹ On the ground of this experiment, von Mosetig advanced the theory that perhaps the pathological cells or their nuclei contain a specific chemical substance, which is able to reduce the aniline dyes in such a way that the latter lose their blue color; in other words, that this at present unknown substance reduces the blue aniline dye to the white, the leukaniline. (When the tumor then has been extirpated and sections have been prepared from it for microscopical examination, the leukaniline in them, being exposed to the oxygen of the air, turns blue again.)

Now, von Mosetig still goes one step further. He says April, 1891): A poisonous chemical product has lately been found in carcinomata by Adamkiewicz, which, inoculated in rabbits, kills them by paralysis of the brain in a few hours. Perhaps this poisonous product reduces the aniline dye and thereby becomes neutralized itself. This again might then explain the consequent regressive fatty metamorphosis and arrest of further growth.

This hypothesis has something very fascinating, provided the new theory on the ætiology of carcinoma could be sustained. This is the theory of Adamkiewicz, namely, that the so-called epithelial (cancer) cell is not a tissue-cell at all, but the cancer-parasite (*coccidium sarcolytus*). This parasite, says Adamkiewicz, produces a poison, "cancroin," with its local effects and its general infection. With this theory as a basis we might thus plausibly explain the curative effect of the aniline dyes; the strong antiseptic quality of pyoktanin

¹ If we put aside a well-corked bottle filled (not entirely) with a deep blue urine of a patient who had taken methyl-blue internally for some time, we will soon see that, beginning at the bottom of the bottle, the color changes from blue to green and then to yellow. After a short while the entire fluid has the normal urine color and all oxygen has been absorbed. If we now open the bottle and leave the fluid exposed to the air, the entire fluid slowly turns blue again, beginning on the upper surface and slowly advancing to the bottom. This procedure may be repeated many times with the same fluid.

paralyzes or destroys (neutralizes) the poisonous effect of the "cancerin," and therewith destroys the work of the cell itself. The cells then undergo fatty degeneration and are reabsorbed, or their remnants are eliminated after perforation of the covering skin, provided they have been destroyed by the dye.

That Adamkiewicz's theory, which had first been enthusiastically commented upon by a number of gentlemen (Bidder, L. Pfeiffer), is not well founded, that his experiments are insufficient and his conclusions deceptive has lately unquestionably and very strongly been shown by Hanseman (*Berliner klinische Wochenschrift*, 1893, No. 28, p. 683) and Paltaux (*Weiner klinische Wochenschrift*, 1893, No. 37, p. 677).

It is further necessary to state that this supposed poison is claimed to have been found in cancerous growths only, and none so far in sarcomata, which also react upon the aniline dyes.

The breaking down with perforation or with reabsorption naturally produces shrinking of the tumor. This is sometimes clearly perceptible by inspection (retraction of the skin due to real cicatrization) or by palpation.¹ In many cases the treatment produces no visible results, especially as stated above in very bloody and soft, rapidly-growing tumors of the bones. But even in injecting them a slower growth is often seen. One gets the impression as if the further spread of the neoplasm were now held in check, as if it were "under control." On the other hand, I have already mentioned that I personally observed a cancer spread and invade other organs with a marvelous rapidity, especially after the treatment had to be interrupted. But there fuchsin had been used. Whether this really had an influence I should not venture to decide.² Other authors report a lasting after-effect of the treatment. Still I believe these cases are exceptional. It will in the majority of cases be the rule that they have to be treated with the aniline dyes until their death.

¹ In two of von Mosetig's patients with cancer of breast, treated with injections, the infiltrated axillary glands slowly decreased in size and disappeared spontaneously. This observation shows that the dye is in part carried away by the lymphatic current and can still influence neoplastic elements which had left the primary focus.

² Burghard also observed "a distinct restraining influence" as long as the injections were made, and a "greatly increased rate of growth as soon as they were discontinued."

Now, Mr. President and gentlemen, if you ask me, did I cure one of my patients with inoperable carcinoma, I have to answer: no. But others have, or at least have succeeded in beneficially influencing large inoperable growths so much, that it might be called "a cure." One of von Mosetig's patients, a gentleman with an immense inoperable adeno-sarcoma of the pelvis, who had been pronounced incurable by many celebrated men abroad, was so far improved by the color-cure that he again entered society. In reading such a report, which two years ago stimulated me to at once begin with this treatment here, one or the other of you may shake his head and murmur: "Error in observation," "passing effect!" But, gentlemen, let me add that von Mosetig saw this patient eight months later and still he was able to note the same improvement. The same author had treated as early as 1883 an inoperable round-cell sarcoma of the right groin of a man, aged fifty, with parenchymatous injections of a 1 per cent. solution of anilinum trichloratum. Eight weeks later the oedema of the lower extremity had disappeared, the large tumor was reduced to a nodule of the size of a walnut, and the ulceration had healed. The patient left the hospital cured and attended to his business. He died of pneumonia one year later. The neoplasm had not recurred. A woman of sixty-six years with an immense myeloid sarcoma of the inferior maxilla of one year's standing received eighty-four injections in all (almost eight ounces of the drug). After seven months' treatment the sarcomatous mass had disappeared, the remaining bony shell was empty. Patient was presented to the Society of Physicians on January 30th and March 13th, 1891. No recurrence after eight months. Nanu, of Bucharest, has reported a number of cases of malignant tumors, where pyoktanin (1 : 3 drachms of a 1 per cent. solution every third day) appears to have effected a cure. Lindner presented a patient to the "Freie Vereinigung der Chirurgen Berlins," on January 9, 1893, with an osteosarcoma of the face, which originally had involved the entire temporal region and a portion of the cheek. Within three months parenchymatous injections of the blue pyoktanin, repeated every third or fourth day, had made it

shrink for about two-thirds of its former size ; the patient's sufferings had ceased. Diakonoff, of Moscow, has come to the conclusion by his observations, "that blue pyoktanin actually possesses a power of destroying malignant new growths, though its action is not energetic." More instances of the same kind could be cited. On the other hand, many only had failures and concluded that the method had "no serious value whatever." Even those who gave the aniline dyes a *fair* trial in the treatment of inoperable carcinoma have no doubt experienced many disappointments. But now and then they were forced to the remark: "No doubt there is something in it." There *are* effects of the injection or application of blue pyoktanin which so far no other drug could produce. Of course, not every case responds favorably. But does every case of tuberculous disease respond favorably to creosote and iodoform?

I abstain from giving any statistics. If anywhere, then here, we need large numbers to draw conclusions. Nobody could so far present them. Von Mosetig gives the histories of ten picked cases out of about seventy, treated in this way. Of the seventy one-third were afflicted with sarcoma, two-thirds with carcinoma. The number of injections varied between 21-125, the amount of pyoktanin used between 21-230 grammes (two-thirds to eight ounces), time of treatment, one to eight months. The ten cases had been greatly improved, two, as it seemed, cured. My own experience is based on about twenty cases. Not of all I could keep track. Some uneducated patients are apt to leave the hospital more rarely our care in private practice), if the result of a continuous, generally slightly painful (puncture and injections) interference does not "rapidly" present favorable results to their eye) Often I have been very favorably impressed by the effect of the treatment, at times I was rather enthusiastic. Still more often I have been disappointed, especially if the treatment had to be discontinued for one or the other reason. Still, according to what I have seen, I fully agree with von Mosetig's conclusion, "that it has been proved by practice, that parenchymatous injections of inoperable malignant growths with pyoktanin can produce disappearance of the malignant tissue—though in exceptional cases

and can heal neoplastic ulcerations." How soon and whether the tumor will recur in favorable cases, can not yet be determined. But if only one out of ten cases were objectively benefited, the treatment deserves trial and should not be at once thrown aside as "ineffective."

Summing up I should say: The use of the aniline dyes in the treatment of inoperable carcinoma (malignant growth) generally is "a palliative treatment," no cure. In *very* rare cases this treatment may cure. Carcinoma and sarcoma of hard type (especially the latter), are better influenced than soft ones; those of the soft tissues easier than of the bones; those with a scanty blood supply more successfully than rapidly growing neoplasms with abundant circulation. The disseminated cancer is no object for the aniline treatment. The treatment with parenchymatous injections requires a perfect knowledge and application of the principles of aseptic and antiseptic surgery. If a doctor does not understand them, or can or will not take time to follow them strictly, I should call out to him: "Hands off; do not try it; you must do harm, and will be disappointed; your tumor will soon suppurate and slough and your patient die of acute or chronic sepsis." Without antiseptics the treatment is bound to harm rather than to do good. It also requires a good deal of patience and perseverance on the part of the surgeon as well as on that of the patient. It will, in the very best case, require a continuous attendance for many weeks or months. On account of the necessary antiseptic precautions the treatment is time-robbing. It will, therefore, in my estimation, only come into favor in the treatment of patients who are able to pay.¹ The poor should be admitted to a hospital. But then we need cancer-hospitals; which have the outspoken purpose to also admit inoperable cases and care for them without regard to the length of the treatment. There it may then be made out, which treatment may possibly best improve the given case, whether the use of the

¹ I personally never begin this treatment without having first properly explained to the patient's relatives what may be expected of it. Dr. Boldt writes me (July 13, 1893), that he has "given up the pyoktanin-treatment of inoperable cases of cancer of the uterus, unless a patient is sent for that particular treatment."

aniline dyes locally, internally and parenchymatously, or inoculation with the coccus erysipelatis (*streptococcus*), if necessary repeated, or perhaps also the subcutaneous injection of neurine. Or we may even anticipate the discovery of some other chemical substance, which shall be able to neutralize the toxins produced by the cancer-cells, provided neurine (Adamkiewicz) should, as it seems, not stand the test. Probably a combination of the methods might deserve preference.

Mr. President and gentlemen, half a year ago, the French physicians and surgeons under the leadership of Duplay, of Paris, united and formed the "Ligue contre le Cancer."¹ Let us follow their example; in this immense country with its thousands of hard working, studying and experimenting physicians, let those who take special interest in the fight against this most dreadful scourge come together and form for the promotion of this special branch of science and for the benefit of suffering mankind, "The American League against Cancer."

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